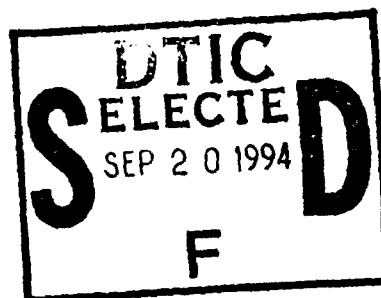
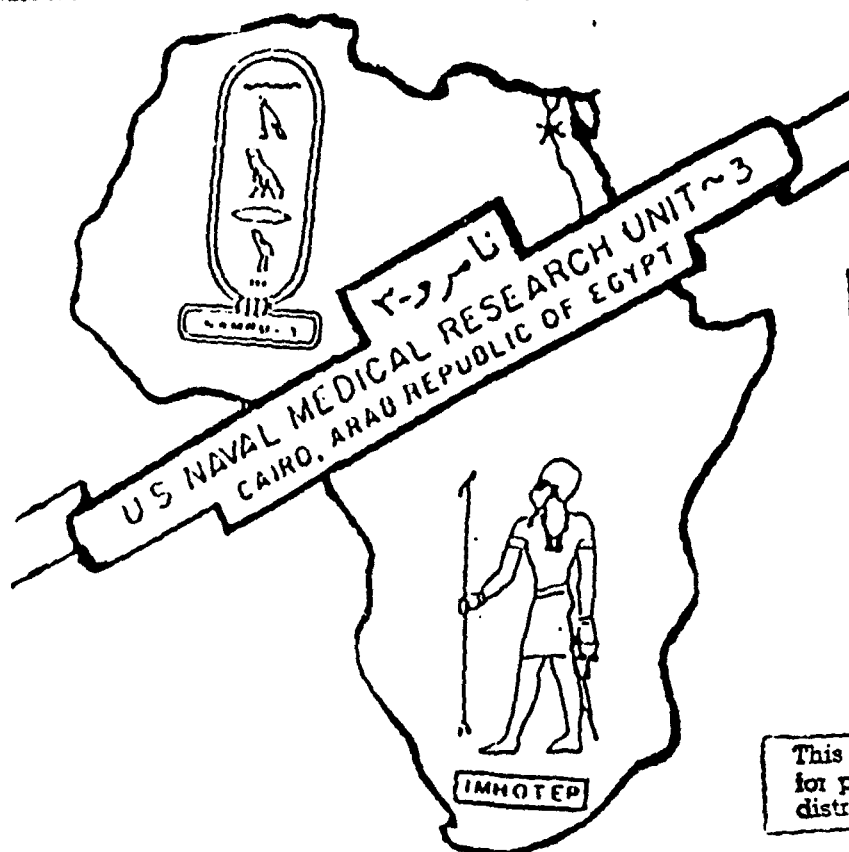


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A DOUBLE-BLIND RANDOMIZED TRIAL OF CEFIXIME COMPARED TO RIFAMPIN
IN THE ERADICATION OF MENINGOCOCCAL PHARYNGEAL
CARRIAGE IN A CLOSED POPULATION

By

Podgore J.K., Girgis N.I., El-Refai M. and Abdel-Moneim A.

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Abstract

Rifampin is recommended as prophylactic treatment for household contacts and closed-group associates of individuals who develop invasive meningococcal infections. A 2 - day course of rifampin in a twice daily 600 mg oral dose is the currently recommended treatment regimen for adults. This study compares the eradication rates of pharyngeal carriage of *Neisseria meningitidis* among Egyptian military recruits with rifampin 2- day therapy and cefixime in a single and 2 - day course of therapy. Two hundred forty seven Egyptian military recruits with *N. meningitidis* pharyngeal carriage living in a closed barracks setting were treated in Cairo between January and April 1990. An additional 85 remained untreated but participated in follow-up cultures. Participating recruits were randomized to either a cefixime 400 mg single dose for two consecutive days, a single 800 mg

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Introduction

Neisseria meningitidis continues to cause outbreaks of disease throughout the world. Despite modern therapy the mortality rate for meningococcal meningitis has remained essentially unchanged during the past 3 decades (McGee and Kaiser, 1990). The development of purified capsular polysaccharide vaccines has been effective in the reduction of meningococcal infection caused by sero-group A and C strains among military recruits and for the control of outbreaks, but currently a commercial vaccine is not available for sero-group B strains which are the predominant infectious strains in many areas of the world (Artenstein et al., 1970 and Greenwood et al., 1978).

The eradication of meningococcal nasopharyngeal carriage using sulfadiazine chemotherapy effectively controlled

* (This work was presented in part at the 1991 Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill.)

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outbreaks of meningococcal disease among military recruits during World War II (Kuhns et al., 1943). This was effective until the early 1960's when emerging sulfadiazine resistant strains became prevalent. Among the numerous antimicrobial agents tested to provide a suitable replacement for sulfadiazine, only rifampin and minocycline proved effective in eliminating meningococcal carriage. Minocycline has been noted in some instances, particularly in the United States, to produce a high incidence of apparent vestibular toxicity (Drew et al. 1976 & Jacobson and Daniel, 1975). Minocycline is not advised in pregnancy and in young children due to potential dental staining (Broome, 1986). Rifampin is currently the drug of choice for chemoprophylaxis for sulfadiazine resistant strains of meningococci (Flynn and Hoperich, 1989). However, rapid emergence of resistant strains noted with the use of rifampin prophylaxis in several large scale outbreaks and the potential for the emergence of resistance among *Mycobacterium spp.* poses significant problems with its use in mass prophylaxis situations (Beam et al., 1975 & Weidmer et al., 1971). Recent studies have reported successful reduction of meningococcal carriage utilizing oral ciprofloxacin or ceftriaxone in a single intramuscular dose (Gaunt and Lambert, 1988 and Schwartz et al., 1988).

The recent availability of cefixime, an oral third generation cephalosporin with *in vitro* activity against *N. meningitidis*, prompted this comparative clinical trial comparing its effectiveness in eradicating nasopharyngeal carriage of meningococci to standard rifampin therapy.

Materials and Methods

The subjects of the study were male Egyptian army recruits aged 18-26 reporting for basic training at a site located on the edge of metropolitan Cairo. The entire recruit camp approximated a relatively closed population that worked, ate, and was quartered in a common barracks area and was not allowed to leave

the camp until after their fourth month of training.

Training companies of approximately 50 per group were selected weekly for periodic routine pharyngeal screening for meningococcal carriage. On the third day after the culture was obtained, subjects having meningococcal strains isolated from their pharynx were solicited for participation in the drug treatment trial. During the period from January to April 1990, 776 army recruits were screened and 43% were positive for pharyngeal meningococcal carriage. Sero-group B comprised 64%, sero-group A 17%, sero-group C 4%, and 15% were non-typable. Two hundred forty seven subjects volunteered to participate in a drug treatment trial. Informed consent was obtained from all participants. The remaining 85 meningococcal carriage positive recruits declined participation in the drug treatment trial but consented to a follow-up throat culture.

Treatment volunteers were randomly assigned to one of three treatment groups consisting of a single oral dose of 800 mg of cefixime, two consecutive single daily doses of 400 mg of cefixime, or rifampin 600 mg twice per day for 2 consecutive days. Placebo tablets were used so that each patient took 2 tablets twice a day for 2 day. Cefixime, rifampin and placebo tablets were enclosed in identical appearing gelatin capsules which were prepared and packaged in coded envelopes by a research pharmacist and the identity of the contents was not disclosed to the subjects or the study physicians. Each dose of medication was administered directly by one of the study physicians in the morning and evening approximately one hour before mealtime. The subjects were asked to report any side effects promptly to the study physicians.

All of the 247 recruits with initial throat cultures positive for *N. meningitidis* were re-cultured 7 days post-treatment or after 10 days in the non-treatment subjects. All throat samples were taken with a dry calcium alginate swab from the posterior wall of the

pharynx by an experienced clinic physician, streaked directly onto Modified Thayer Martin agar plates and transported to the laboratory within two hours for incubation at 36°C in 7% CO₂ for 72 hours. Suspect *N. meningitidis* colonies were identified by standard techniques (Morello et al., 1985). At the time of the follow-up culture the treatment subjects were examined and administered a drug reaction questionnaire by a study physician.

Results

Of the 94 subjects that received rifampin 2 had *N. meningitidis* isolated from the pharynx 7 days post-treatment, resulting in a 98% reduction of carriage. Of the 81 subjects receiving 2 consecutive single daily doses of 400 mg cefixime, 4 were positive for meningococcal carriage at 7 days post-treatment yielding a 95% reduction in carriage. There is no statistically significant difference in the effectiveness of these 2 treatment regimens (table-1). However, in the 72 subjects that received a single 800 mg dose of cefixime, 18 remained positive 7 days post-treatment for a 75% carriage reduction which was

of 2 consecutive single daily oral doses of 400 mg of cefixime was as effective as standard rifampin therapy for the eradication of meningococcal carriage and was associated with minimal side effects.

significantly less effective than the other treatment regimens in eradicating meningococcal carriage. In the untreated group 51 of 85 were meningococcal carriage positive 10 days after the initial culture. All initial and post-treatment meningococcal isolates were sensitive to rifampin and cefixime, although 64% of the strains were resistant to sulfadiazine. Side-effects based on subject complaints and responses to the post-treatment questionnaire occurred in approximately 30% of the subjects in each treatment group (table-2). Loose stools and headache were the most frequent symptoms occurring in 10 to 20 percent of all treatment groups. Nausea occurred significantly ($P = <0.001$) more frequently in the single dose cefixime regimen. All symptoms lasted less than 48 hours and were not severe enough to interrupt normal daily activities.

In this clinical treatment trial a course

Table-1: Efficacy of treatment regimens in the eradication of pharyngeal *N. meningitidis* carriage.

Treatment Regimen (number treated)	No. Positive on Reculture	Carriage Reduction
Cefixime 400mg x 2 days (81)	4/81 ^a	95%
Cefixime 800mg x 1 day (72)	18/72 ^b	75%
Rifampin 600mg bid x 2 days (94)	2/94 [*]	93%
Non treatment (85)	51/85	----

^aThere was no statistically significant difference between these two treatment regimens

^bCefixime 800mg x 1 day versus rifampin and cefixime 400mg x 2 days: * $P = <0.001$

Table- 2: Side effects of treatment regimens for the eradication of pharyngeal *N. meningitidis* carriage.

Side effects	Cefixime 400mg x 2 days (n = 81)	Cefixime 800mg x 1 day (n = 72)	Rifampin 600mg bid x 2 days (n = 94)
Nausea	0	11 ^a	4
Abdominal pain	9	15	14
Vomiting	0	1	0
Loose stools	18	16	10
Diarrhea	4	6	6
Headache	9	16	18
Rash	0	4	0

^aP = <0.001

Discussion

Outbreaks of meningococcal disease continue to pose a threat in many areas throughout the world. Particularly the problem of epidemics occurring in closed - population settings such as military barracks, refugee camps, orphanages, and institutions for the disabled continues to be a serious public health issue. Rifampin and minocycline have both been used extensively in these situations. However, information on these agents from several studies have demonstrated significant problems associated with their use in mass prophylaxis programs. The several reports of emergent resistant strains of *N. meningitidis* occurring during mass prophylaxis with rifampin limits its use in this situation when other effective therapeutic agents are available (Beam et al., 1975 and Weidmer et al., 1971). The simple single daily oral dosage regimen of 400 mg of cefixime for 2 days offers a satisfactory alternative to rifampin for mass meningococcal prophylaxis in a closed - population setting. Cefixime affords the advantage over rifampin in that it is available in a stable liquid suspension as well as tablet form and is approved for therapy during pregnancy. The 400 mg oral dose appears to be well tolerated. There was no evidence in this trial or in published reports of the emergence of

cefixime resistant strains, although this potential should continue to be carefully monitored.

Until the successful development of a vaccine for sero-group B strains of *N. meningitidis* the control of outbreaks of meningococcal disease will continue to be a problem in closed-population settings. Cefixime may prove to be a suitable prophylactic antimicrobial agent in this situation.

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